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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,711	01/24/2000	David S. Roberts	PC10299A	6167

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/489,711	Roberts et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 14, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-23* is/~~are~~ pending in the application.

4a) Of the above, claim(s) *19-23* is/~~are~~ withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12-18* is/~~are~~ rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicant's amendment filed 05/14/02 (paper no. 12) in response to the non-final Office Action mailed 12/11/01 (paper no. 10). With this, Applicants have amended the specification.

Misnumbered Claim

2) The numbering of claims is not in accordance with 37 C.F.R 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 19 has been renumbered as claim 23.

Status of Claims

3) No claims have been amended via the amendment filed 05/14/02.

New claim 19, now renumbered under Rule 126 as claim 23, has been added via the amendment filed 05/14/02.

Claims 12-23 are pending.

Claim 23 has been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 12-18 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in 6 of the Office Action mailed 12/11/01 (paper no. 10) is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Withdrawn

7) The rejection of claims 12, 13, 16 and 17 made in paragraph 8 of the Office Action mailed 12/11/01 (paper no. 10) under 35 U.S.C § 102(b) as being anticipated by Sato *et al.* (*Vet. Microbiol.* 43(2): 173-182, 1995 - Applicants' IDS), is withdrawn in light of the modified rejection made below.

8) The rejection of claims 12 and 14-16 made in paragraph 9 of the Office Action mailed 12/11/01 (paper no. 10) under 35 U.S.C § 102(b) as being anticipated by Sawada *et al.* (*Am. J. Vet. Res.* 48: 239-242, 1987 - Applicants' IDS) as evidenced by Oaks *et al.* (US 6,277,379), is withdrawn in light of the modified rejection made below.

9) The rejection of claims 12, 17 and 18 made in paragraph 11 of the Office Action mailed 12/11/01 (paper no. 10) under 35 U.S.C § 103(a) as being unpatentable over Dayalu *et al.* (WO 91/18627) in view of Sato *et al.* (*Vet. Microbiol.* 43(2): 173-182, 1995 - Applicants' IDS) and Wild RL (*J. Am. Vet. Med. Assoc.* 184: 944-949, 1984), is withdrawn in light of the modified rejection made below.

Response to Applicants' Arguments

10) Applicants contend that the aluminum phosphate gel used in the immunogen preparation of the Sato reference is not added as a stabilizing agent, but as an adjuvant to test for the immunogenicity of the culture supernatant fractions. Applicants assert that the present invention utilizes aluminum phosphate gel as a stabilizing agent in order to 'maintain the antigenic potential of a fluid fraction of an *E. rhusiopathiae* culture or otherwise slow the degradation of its antigenic potential after removal of the bacteria'. Applicants contend that absent a showing in Sato *et al.* that aluminum phosphate gels are used as stabilizing agents, "the only use of aluminum phosphate gels known to those of skill in the art is for adjuvant purposes". Applicants argue that Sato *et al.* teach the addition of the aluminum phosphate gels long after obtaining the fluid fractions of the *E. rhusiopathiae* culture, whereas the instant invention provides for the addition of the stabilizing agent, such as, aluminum phosphate gel, calcium phosphate gel, etc.,

immediately after the supernatant fraction is taken from the fluid fraction of the *E. rhusiopathiae* culture.

Applicants' arguments have been carefully considered, but are non-persuasive. As drafted currently, instant claims encompass an antigen composition comprising a fluid fraction from an *E. rhusiopathiae* culture and a stabilizing agent, such as, aluminum phosphate gel, added long after obtaining the fluid fractions of the *E. rhusiopathiae* culture, and immediately after the supernatant fraction is taken from the fluid fraction of the *E. rhusiopathiae* culture. The time of addition of the stabilizing agent is irrelevant in the claims as currently presented. Furthermore, all the structural elements required to be present in the claimed antigen composition are taught by Sato *et al.* The two structural elements that are required to be present in the instantly claimed antigen composition include: a) A fluid fraction from an *E. rhusiopathiae* culture; and b) An aluminum phosphate gel. Both of these structural components are met by Sato's teachings. The Office's position that Sato's composition is the same as the Applicants' composition is based upon the fact that every characteristic overlapping in the Sato's and Applicants' disclosures are the same. In spite of the fact that Sato *et al.* are silent about the stabilizing function of the aluminum phosphate gel, there is complete structural overlap to reasonably conclude that Sato's composition is one and the same as the Applicants' composition. Since the prior art aluminum phosphate gel is structurally the same as the aluminum phosphate gel present in the instantly claimed antigen composition, it is expected to have the intrinsic or inherent stabilizing function. The property of being able to serve as a stabilizing agent as recited by the Applicants is an inseparable property inherent to Sato's aluminum phosphate gel. It was well known in the state of the art at the time of the invention that aluminum hydroxide and aluminum phosphate served as stabilizing agents in addition to serving as adjuvants. See the applied art and/or the 'Relevant Prior Art' section below.

With regard to the teachings of Sawada *et al.*, Applicants contend that Sawada *et al.* use formalin for killing *E. rhusiopathiae* and not as a stabilizing agent. Applicants assert that Oaks *et al.* teach the use of formalin as a common preservative and not as stabilizing agent in antigen or vaccine compositions. Applicants state that the Office Action uses the term 'stabilizing agent' and 'preservative' interchangeably. Applicants' arguments have been carefully considered, but

are partly persuasive. The reference to a preservative is withdrawn in the modified rejection made below. Contrary to the Applicants' contention, at the time of the instant invention, it was well known in the art that formalin also served as stabilizing agent. For instance, Neurath (US 3,962,421) as well as Collier *et al.* (US 4,709,017) taught formalin as a stabilizing agent in vaccine formulations. See column 4, line 32 of Neurath; and column 1, lines 48-50 of Collier *et al.* Thus, all the structural elements required to be present in the claimed antigen composition are taught by Sawada *et al.* The two structural elements that are required to be present in the instantly claimed antigen composition include: a) A fluid fraction from an *E. rhusiopathiae* culture; and b) A stabilizing agent. Both of these structural components are met by Sawada's teachings. The Office's position that Sawada's composition is the same as the Applicants' composition is based upon the fact that every characteristic overlapping in the Sawada's and Applicants' disclosures are the same. In spite of the fact that Sawada *et al.* are silent about the stabilizing function of formalin, there is complete structural overlap to reasonably conclude that Sawada's composition is one and the same as the Applicants' composition. Since the prior art formalin is the same as the formalin present in the instantly claimed antigen composition, it is expected to have the intrinsic or inherent stabilizing function. The property of being able to serve as a stabilizing agent as recited by the Applicants is an inseparable property inherent to Sawada's formalin. It was well known in the state of the art at the time of the invention that formalin served as a stabilizing agent in addition to serving as an inactivating agent. See the applied art and/or the 'Relevant Prior Art' section below.

With regard to the teachings of Dayalu *et al.*, Applicants contend that Dayalu *et al.* disclose a vaccine composition comprising an *E. rhusiopathiae* antigen extract and merthiolate (i.e., thimerosal) as a preservative, and that Dayalu *et al.* are silent about whether or not the antigen extract is a fluid fraction from *E. rhusiopathiae* culture. Applicants correctly point out that the secondary reference applied is of Wild RL and not of Wood RL as indicated in the Office Action. Applicants assert that the instant invention is distinct from the antigen/vaccine composition of Sato *et al.* for the reasons discussed above. Applicants further assert that MERTHIOLATE or thiomerosal is an antiseptic or a preservative as opposed to a stabilizing agent. Applicants argue that there is neither a suggestion in the prior art references themselves,

nor any motivation to combine the teachings of the cited references. Applicants' arguments have been carefully considered, but are partly persuasive. The reference to a preservative is withdrawn in the modified rejection made below. Contrary to the Applicants' contention, at the time of the instant invention, it was known in the art that thimerosal also served as stabilizing agent. For instance, Eckhardt *et al.* (US 5,895,655) taught thimerosal to serve as a stabilizer in a bacterial vaccine (see claim 6). Furthermore, Dayalu's composition also contained aluminum hydroxide or Tween 80, both of which were known in the art to serve as stabilizing agents. For instance, Barenholz *et al.* (US 6,156,337) taught the dual role of aluminum hydroxide, both as an adjuvant and as a stabilizer in microbial vaccines (see column 13, last two lines). Fukuda disclosed the use of TWEEN 80 as a stabilizer in vaccine compositions (see column 7, first full paragraph). Similarly, Volkin *et al.* taught Tween 80 to provide increased stabilization of the vaccine components (see column 7, fourth full paragraph). Furthermore, with regard to the alleged absence of suggestion in the prior art or absence of motivation, the test for obviousness is not that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, Wood guides one skilled in the art to choose culture filtrate by expressly teaching that most of the immunizing antigen is found in the culture filtrate (i.e., fluid fraction) of *Erysipelothrix rhusiopathiae*.

Rejection(s) under 35 U.S.C. § 102

11) Claims 12, 13, 16 and 17 are rejected under 35 U.S.C § 102(b) as being anticipated by Sato *et al.* (*Vet. Microbiol.* 43(2): 173-182, 1995 - Applicants' IDS) as evidenced by Petre *et al.* (US 6,013,264, filed 21 May 1993).

Sato *et al.* taught an antigenic composition comprising a culture filtrate antigen of *Erysipelothrix rhusiopathiae* culture (i.e., fluid fraction). The culture filtrate was fractionated and concentrated by ultrafiltration and mixed with aluminum phosphate gel, i.e., stabilizing agent. The antigen fraction was mixed with an adjuvant. The composition was injected into mice. That the process of ultrafiltration concentrates the fluid fraction of the culture by about 3 to about 30-fold is inherent from the teachings of Sato *et al.* That the prior art aluminum

phosphate gel possessed the intrinsic stabilizing function is inherent from the teachings of Sato *et al.* in light of what was well known in the art. For instance, Petre *et al.* taught that aluminum phosphate, in soluble or gel form, serves as a conventional stabilizing agent in a vaccine composition in addition to serving as an adjuvant (see abstract; column 2, lines 19-23 and 46-62; column 5, lines 45-55). Thus, all the structural elements required to be present in the claimed antigen composition are taught by Sato *et al.* The two structural elements that are required to be present in the instantly claimed antigen composition include: a) A fluid fraction from an *E. rhusiopathiae* culture; and b) An aluminum phosphate gel. Both of these structural components are met by Sato's teachings. The Office's position that Sato's composition is the same as the Applicants' composition is based upon the fact that every characteristic overlapping in the Sato's and Applicants' disclosures are the same. In spite of the fact that Sato *et al.* are silent about the stabilizing function of the aluminum phosphate gel, there is complete structural overlap to reasonably conclude that Sato's composition is one and the same as the Applicants' composition. Since the prior art aluminum phosphate gel is structurally the same as the aluminum phosphate gel present in the instantly claimed antigen composition, it is expected to have the intrinsic or inherent stabilizing function. The property of being able to serve as a stabilizing agent as recited by the Applicants is an inseparable property inherent to Sato's aluminum phosphate gel. It was well known in the state of the art at the time of the invention that aluminum hydroxide and aluminum phosphate served as stabilizing agents in addition to serving as adjuvants.

The disclosure of Sato *et al.* anticipates the instant claims. Petre *et al.* is **not** used as a secondary reference in combination with Sato *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Sato *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

12) Claims 12 and 14-16 are rejected under 35 U.S.C § 102(b) as being anticipated by Sawada *et al.* (*Am. J. Vet. Res.* 48: 239-242, 1987 - Applicants' IDS) as evidenced by Neurath (US 3,962,421) or Collier *et al.* (US 4,709,017).

Sawada *et al.* taught an antigenic composition comprising a supernatant fluid (i.e., fluid fraction) obtained from an *Erysipelothrix rhusiopathiae* culture which was inactivated with formalin and concentrated to 10% of its initial volume (see paragraph bridging pages 239 and

240). That formalin acted as a stabilizing agent is inherent from the teachings of Sawada *et al.* in light of what was well known in the art. For instance, Neurath or Collier *et al.* taught formalin to be a stabilizing agent in antigen or vaccine compositions. See column 4, line 32 of Neurath; and see column 1, lines 48-50 of Collier *et al.* Thus, all the structural elements required to be present in the claimed antigen composition are taught by Sawada *et al.* The two structural elements that are required to be present in the instantly claimed antigen composition include: a) A fluid fraction from an *E. rhusiopathiae* culture; and b) A stabilizing agent. Both of these structural components are met by Sawada's teachings. The Office's position that Sawada's composition is the same as the Applicants' composition is based upon the fact that every characteristic overlapping in Sawada's and Applicants' disclosures are the same. In spite of the fact that Sawada *et al.* are silent about the stabilizing function of formalin, there is complete structural overlap to reasonably conclude that Sawada's composition is one and the same as the Applicants' composition. Since the prior art formalin is structurally the same as the formalin present in the instantly claimed antigen composition, it is expected to have the intrinsic or inherent stabilizing function. The property of being able to serve as a stabilizing agent as recited by the Applicants is an inseparable property inherent to Sawada's formalin. It was well known in the state of the art at the time of the invention that formalin served as a stabilizing agent in addition to serving as an inactivating agent.

The disclosure of Sawada *et al.* anticipates the instant claims. Neurath or Collier *et al.* is **not** used as a secondary reference in combination with Sawada *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Sawada *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Rejection(s) under 35 U.S.C. § 103

13) Claims 12 and 16-18 are rejected under 35 U.S.C § 103(a) as being unpatentable over Dayalu *et al.* (WO 91/18627, already of record) in view of Sato *et al.* (*Vet. Microbiol.* 43(2): 173-182, 1995 - Applicants' IDS), Wood RL (*J. Am. Vet. Med. Assoc.* 184: 944-949, 1984, already of record) and Eckhardt *et al.* (US 5,895,655, 11 July 1990), or Barenholz *et al.* (US 6,156,337, 09 September 1996), or Fukuda (US 6,11,089, 28 February 1997), or Volkin *et al.* (US 6,358,744, filed 08 April 1997).

The reference of Eckhardt *et al.*, Barenholz *et al.*, Fukuda or Volkin *et al.* is applied in this rejection, because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

Dayalu *et al.* disclose a vaccine composition comprising an *Erysipelothrix rhusiopathiae* antigen extract (see page 11; and claims 18 and 19). The vaccine comprises merthiolate, i.e., stabilizing agent (see page 17, last paragraph). The vaccine comprises a conventional adjuvant, such as, Amphigen, mineral oil and lecithin, aluminum hydroxide etc. (see page 12). Sterile mineral oil (Drakeol) containing 5-40% of lecithin, 0.7 - 32.0% Tween 80 (i.e., amphiphilic surfactant) are contained in the vaccine composition (see paragraph bridging pages 17 and 18). It is implicit that the percent concentrations of lecithin, oil and amphiphilic surfactant recited in claim 18 falls in the concentration ranges taught by Dayalu *et al.*

Dayalu *et al.* are silent about whether or not the antigen extract is a fluid fraction from the *Erysipelothrix rhusiopathiae* culture.

The teachings of Sato *et al.* are explained above.

Wood expressly teaches that most of the immunizing antigen is found in the culture filtrate of *Erysipelothrix rhusiopathiae* (see page 948, left column).

That merthiolate, i.e., thimerosal, aluminum hydroxide or Tween 80 inherently served as a stabilizer in prior art vaccine is implicit from the teachings of Dayalu *et al.* in light of what was known in the art. For instance, Eckhardt *et al.* taught thimerosal to serve as a stabilizer in a bacterial vaccine (see claim 6). Barenholz *et al.* taught the dual role of aluminum hydroxide both as an adjuvant and as a stabilizer in microbial vaccines (see column 13, last two lines). Fukuda disclosed the use of TWEEN 80 as a stabilizer in vaccine compositions (see column 7, first full paragraph). Similarly, Volkin *et al.* taught Tween 80 to provide increased stabilization of the vaccine components (see column 7, fourth full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the *Erysipelothrix rhusiopathiae* antigen extract in Dayalu's vaccine composition with Sato's culture filtrate antigen of *Erysipelothrix rhusiopathiae* culture (i.e., fluid fraction) to produce the vaccine composition of the instant invention with a reasonable expectation of success. One skilled in the art would have been motivated to produce the instant

invention for the expected benefit of providing, advantageously or selectively, a vaccine composition that comprises most of the immunizing antigens of *Erysipelothrix rhusiopathiae* as taught by Wood. Substituting one antigenic composition in a vaccine with another, alternative, art-known antigenic composition that comprises most of the immunizing antigens of *Erysipelothrix rhusiopathiae* would have been obvious to one skilled in the art and would have brought about similar results.

Claims 12 and 16-18 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

14) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Rappuoli (*Vaccine* 12: 579-581, 1994) taught formaldehyde to be a bacterial "antigen stabilizer" (see page 579, right column).
- Matsudsa (US 6,372,225, filed 24 September 1997) taught that conventional detoxifying agents, such as, formalin, glutaraldehyde, beta-propiolactone and the like also serve as stabilizing agents or fixatives in bacterial antigen compositions (see column 13, lines 26-33).

Remarks

15) Claims 12-18 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER